REMARKS

Status of Application and Claim Amendments

This Request for Continued Examination is filed in accordance with 37 C.F.R. §§ 1.114 and 1.198 (see M.P.E.P. § 1214.07) following a Decision on Appeal by the Board of Patent Appeals and Interferences.

Claims 20-34 and 39-58 are currently pending. Applicants herein cancel claims 18-19 and 35-38, which were subject to appeal, and submit new claims 39-58. Claim 39 serves to amend previously pending claim 18 by incorporating the subject matter of previously pending claim 37. Claims 40-44 recite longer time periods and/or more restrictive percentages of retained thrombin activity after storage than that recited in claim 39. Claim 49 similarly serves to amend previously pending claim 19. Claims 50-54 recite longer time periods and/or more restrictive percentages of retained thrombin activity after storage than that recited in claim 49.

Support for those amendments may be found, *inter alia*, at page 3 of the specification, first full paragraph; page 6, line 16, to page 7, line 4; and also in Tables 4-5. (For example, see formulations 8 and 9, which contain exemplary noncovalently binding inhibitors of thrombin activity and which maintain 90-100% activity after 12 months of storage in the liquid state at 20-25 °C, and which also retain 90.1% and 82.4% activity respectively after 24 months of storage in the liquid state at 20-25 °C.

Dependent claims 45-46 and 55-56 recite particular types of noncovalently binding inhibitors of thrombin activity, while claims 47 and 57 recite particular pH's. Those claims are supported, for example, at page 5, lines 4-7 and last line; at page 6, line 16, to page 7, line 4; as well as in Tables 4-5.

Dependent claims 48 and 58 recite that the polyalcohol percentage does not exceed 2% (w/v). Those claims are also supported at page 3, lines 11-14, and in Tables 4-5. See, for example, numbers 8 and 9 of Table 4 containing 2% (w/v) of the polyalcohol mannitol, and numbers 1, 4, 6, and 12, containing no polyalcohol, and number 11, containing 1% (w/v) mannitol.

As described below, the new claims are neither anticipated nor made obvious by the cited art. Applicants therefore respectfully request their entry.

Claims 20-34, drawn to processes of making and using thrombin preparations, remain withdrawn. Applicants have amended those claims solely to depend them from the new claims 39-58. Applicants continue to request their rejoinder upon allowance of the product claims 39-58, according to the practice of M.P.E.P. § 821.04 and 37 C.F.R. § 1.141.

Claims 39-58 are Novel

A novelty rejection under 35 U.S.C. § 102(b) of former claims 18, 35, and 37 was considered by the Board of Patent Appeals and Interferences on March 18, 2005. In the Decision on Appeal, the Board concluded that claim 18 was not novel over articles by Lorne et al. and Allary et al. See Lorne et al. (*Rev. Fr. Transfus. Hemobiol.* 32: 391-400 (1989)) and Allary et al. (*Ann. Pharmaceutiques Francaises* 48: 129-35 (1990)). However, the Board did not consider the additional limitation of dependent claim 37 that the preparation be stable for a minimum of 12 months at 20-25 °C such that the thrombin activity retains at least 70% of its original value. Instead, the Board concluded expressly that "we do not [interpret claim 18] to require that the preparation be stable when stored in a liquid form." (Decision on Appeal at page 7, lines 6-7.)

Applicants have now included that limitation in claims 39 and 49, and have filed a number of dependent claims reciting stricter stability requirements, exemplary noncovalent inhibitors of thrombin activity, and a maximum concentration of 2% (w/v) polyalcohol. For example, Table 4 shows that preparations according to the present invention containing noncovalent inhibitors of thrombin activity (preparations 8 and 9) remain about 90-100% active after 12 months of storage at 20-25 °C in a liquid preparation, and remain about 82-90% active after two years of storage under those conditions. In contrast, preparations without the added inhibitors, but containing stabilizers such as high concentrations of NaCl, amino acids, and viscosity-enhancing sugar alcohols, only remain between about 43% to 65% active after 12 months of storage at 20-25 °C in the liquid state. (See Tables 4 and 5 of the instant application.)

The cited art does not expressly or inherently teach preparations meeting the limitations of claims 39 or 49. As the instant application describes, "none of the processes disclosed to date [produces] a purified, calcium-ion containing, virus-safe thrombin preparation which is stable in the liquid state at 0 °C and higher temperatures, and whose thrombin activity after 12 months or more is still over 70-80% of the initial level." (Specification at page 3, lines 5-10.) Indeed, the Lorne and Allary articles do not teach or suggest preparations of thrombin that retain stability as recited in either claim 39 or 49.

Claims 39-58 are Nonobvious

The instant claims 39-58 are also nonobvious over the prior art.

A *prima facie* case of obviousness must meet the following three requirements: (1) all of the claim limitations must be taught or suggested; (2) there must be an

objective teaching in the prior art, and not in the applicant's disclosure, to combine or modify the art; and (3) the prior art must teach a reasonable expectation of success in performing that combination or modification. (See M.P.E.P. §§ 2141-2143.)

In its Decision on Appeal, the Board considered only the subject matter of claim 18 in light of the cited publications by Lorne and Allary (discussed above) and by Hanada, Brezniak, and Altshuler. (United States Patent No. 5,945,103; *Blood Coag. and Fibrinolys.* 5: 847-8 (1994); and United States Patent No. 4,363,319, respectively.) The Board therefore did not consider all of the limitations of claims 39, 49, and of the dependent claims presented herein. (See the Decision on Appeal at pages 8-9.)

The above combination of publications does not teach all of the limitations of new claims 39-58. For example, Lorne and Allary do not teach or suggest preparations comprising thrombin as well as a noncovalently binding inhibitor of thrombin activity that remain active after extended periods of storage at 20-25 °C in the liquid state. Instead, Lorne and Allary teach methods of extracting thrombin from unpure solutions using chromatography. Lorne and Allary state that the thrombin should be stored in purified form by lyophilization and teach removing all traces of thrombin inhibitors and other buffer ingredients from the chromatography process specifically for that purpose. Hanada, Brezniak, and Altshuler do not bridge the gap left by Lorne and Allary.

Both Brezniak and Altshuler are silent as to noncovalently binding inhibitors of thrombin. Hanada does not teach storing thrombin solutions, but teaches only another method of obtaining pure thrombin by chromatography and associated chemical or heat treatments. (*See* Example 1 at col. 5.) While benzamidine is added during one of the intermediate-stage chemical treatments and is subsequently removed, Hanada does not

provide any objective teaching that benzamidine or other noncovalently binding inhibitors of thrombin activity would increase the stability of thrombin during long storage periods at room temperatures. (*See Id.*, and col. 4, lines 13-28.) In addition, Hanada, like Lorne and Allary, teaches that thrombin preparations that might be used therapeutically should be protected and stored by lyophilization in the absence of thrombin inhibitors or other chemical additives beyond simple buffer ingredients. (*See* col. 5, lines 45-50.)

In light of these remarks, Applicants respectfully request the allowance of claims 39-58, and the rejoinder of the method claims 20-34 which depend on claims 39 and 49.

Please grant any extensions of time necessary to enter this Amendment and Request for Continued Examination. If there is any fee due in connection with the filing of this Amendment that is not otherwise found herewith, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: _____
Elizabeth A. Doherty
Reg. No. 50,894